

PATENT SPECIFICATION

(11) 1267583

NO DRAWINGS

33
32
31
30
29
28
27
26
25
24
23
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1

- (21) Application No. 30873/69 (22) Filed 18 June 1969
(31) Convention Application No. 738425 (32) Filed 20 June 1968 in
(33) United States of America (US)
(45) Complete Specification published 22 March 1972
(51) International Classification C 07 d 27/C4//C 07 c 125/C9
(52) Index at acceptance

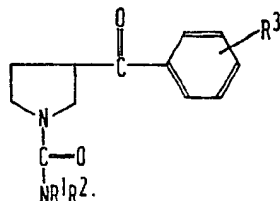


C2C 171—191—280 183—188—289 1Q11G 1Q11J 1Q4
1Q6C 1Q7A 1Q8A 1Q9B 215 220 225 22Y 247
250 251 25Y 30Y 311 313 31Y 338 339 342 347
34Y 351 355 3A14A3D 3A14A5 3A14A7A
3A14A8D 574 577 584 594 627 62X 694 697
71Y 790 79Y KA KS

(54) 1-CARBAMOYL-3-AROYLPYRROLIDINES

(71) We, A. H. ROBINS COMPANY, INCORPORATED, a Corporation organised and existing under the Laws of the State of Virginia, United States of America, of 1407 Cummings Drive, Richmond Virginia, 23220, United States of America do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to 1 - carb - amoyl - 3 - aroylpyrrolidines, and to a process for their preparation.
1 - carbamoyl - 3 - aroylpyrrolidines according to the invention are represented by the following general structural formula:



Formula I

wherein:
R¹ and R² each represent hydrogen, lower alkyl, lower cycloalkyl or aryl; and
R³ represents hydrogen, fluorine, chlorine, bromine, lower alkyl or trifluoromethyl. The invention also embraces acid addition salts of these compounds.
In the definition of the symbols in Formula 1 and where they appear elsewhere throughout this specification the following terms have the meanings indicated:
The term "lower alkyl" means straight or branched chain radicals of up to eight carbon atoms inclusive, preferably no more than six carbon atoms, and is exemplified by such

[Price 25p]

groups as methyl, ethyl, propyl, isopropyl, butyl, sec. butyl, tertiary butyl, amyl, isoamyl, hexyl, heptyl and octyl.

The term "lower cycloalkyl" means cyclic radicals containing three up to nine carbon atoms inclusive and encompasses such groups as cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, methylcyclohexyl, ethylcyclopentyl, cycloheptyl and cyclooctyl.

An "aryl" radical refers to the unsubstituted phenyl radical or to a phenyl radical substituted by any radical or radicals which are not reactive or otherwise interfering under the conditions of reaction, such radicals including lower alkoxy, lower alkyl, trifluoromethyl and halo. The aryl radicals have preferably no more than one to three substituents such as those given above and, furthermore, these substituents can be in the various available positions of the aryl nucleus and, when more than one substituent is present, can be the same or different and can be in various position combinations relative to each other.

An "aroyl" radical has the formula
 $\begin{array}{c} \text{O} \\ \parallel \\ \text{—C—aryl.} \end{array}$

The compounds of the invention have useful pharmacodynamic activity. More specifically, the compounds of the invention have anticonvulsant activity as measured by standard pharmacological procedures in animals. Exemplary of the activity shown by the compounds of this invention after intraperitoneal injection in mice is the abolition of the tonic extensor component of the seizure pattern against corneal stimulation using the recognized supramaximal electro-shock seizure technique of Toman J. E. P. et al., J. Neurophysiol 9, 47 (1946).

The preferred compounds of the present invention and their ED₅₀ values expressed in terms of mg/kg determined in mice by the

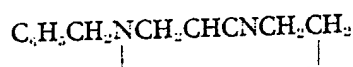
BEST AVAILABLE COPY

procedure described hereinabove are as follows:

- Example 4 ED₅₀ 88 mg/kg
 Example 5 ED₅₀ 100 mg/kg
 5 Example 10 ED₅₀ 75 mg/kg
 Example 6 ED₅₀ 80 mg/kg

The compounds of the invention may be prepared by the following series of steps:

- (1) A 1 - benzyl - 3 - cyanopyrrolidine of the formula:

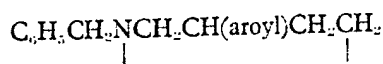


prepared as described in United States Patent Specification No. 3,318,908 is reacted with an arylmagnesium halide of the formula:

- 15 Aryl—Mg—X

wherein X is chlorine or bromine, e.g. with a slight excess of the arylmagnesium halide under the reaction conditions generally used when carrying out a Grignard reaction using anhydrous ether as the reaction medium. The reaction complex following the reaction period is decomposed using dilute caustic solution to give a 1 - benzyl - 3 - aroylpyrrolidine.

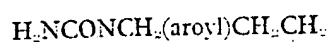
- (2) The 1 - benzyl - 3 - aroylpyrrolidine of the formula:



prepared as in Step 1 is then reacted with cyanogen bromide, e.g. with a slight excess of cyanogen bromide in a dry inert solvent, illustratively, chloroform; the solvent is evaporated after the reaction is completed.

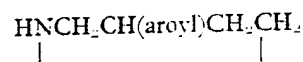
(3) the 1 - cyano - 3 - aroylpyrrolidine thus obtained is hydrolyzed using dilute hydrochloric acid, e.g. without further purification or isolation by refluxing with 4N hydrochloric acid, to a 1 - carbamoyl - 3 - aroylpyrrolidine which is within the scope of this invention as represented by Formula 1 above (R¹ and R² both hydrogen). To produce compounds of Formula 1 where at least one of R¹ and R² is other than hydrogen, the following additional steps may be performed.

- (4) The 1 - carbamoyl - 3 - aroylpyrrolidine of the formula:



prepared as in Step 3 is hydrolyzed to a 3 - aroylpyrrolidine using concentration hydrochloric acid, e.g. by prolonged refluxing for a period of about 48 hours to about 72 hours. In a modified procedure the 3 - aroylpyrrolidines can be obtained directly from the residual 1 - cyano - 3 - aroylpyrrolidines prepared as in Step 2 by refluxing the material in concentrated hydrochloric acid for periods up to 72 hours.

- (5) The 3 - aroylpyrrolidines of the formula:



prepared as in Step 4 are then reacted with various reactants including lower alkyl isocyanates, aryl isocyanates, N-lower cycloalkyl-N-arylcarbamoyl halides, N,N-di-lower alkyl carbamoyl halides, and N,N-diaryl carbamoyl halides to give further novel compounds of the present invention embraced by Formula 1.

1 - Benzyl - 3 - aroylpyrrolidine (Step 1) and 3 - aroylpyrrolidines (Step 4) are claimed in co-pending British patent application No. 30872/69.

The acid addition salts of the base compounds of Formula 1 can be prepared therefrom by conventional procedures.

The following Examples illustrate the invention, except that Examples 1—3, 7—9 and 11—13 relate to the preparation of intermediates.

EXAMPLE 1

1 - Benzyl - 3 - benzoylpyrrolidine hydrochloride hydrate.

To a stirred solution of 544 g. (3.0 moles) of phenyl-magnesium bromide in 1.5 litres of dry ether was added 279 g. (1.5 moles) of 1 - benzyl - 3 - cyanopyrrolidine in 400 ml. of dry ether at a rate which maintained gentle refluxing. The mixture was stirred for two hours at room temperature after the addition was complete, cooled and treated with 151 g. (3.0 moles) of ammonium chloride in 900 ml. of water. After the ether was evaporated the aqueous suspension was heated on a steam bath for several hours to ensure hydrolysis of the ketimine. The mixture was then extracted with ether and the combined extracts were washed with water and dried over magnesium sulphate. The solvent was evaporated and the residual oil distilled at reduced pressure. The light yellow oil boiling at 172—175° C./0.08 mm. weighed 210 g. (53% yield). A portion of the free base (6 g.) was treated with 3N HCl and the white crystalline hydrochloride which formed was crystallized from water.

The salt weighed 2.6 g. and melted at 116—118.5° C.

Analysis: Calculated for $C_{18}H_{22}NO_2Cl$:
C, 67.59; H, 6.93; N, 4.38

5 Found: C, 67.85; H, 6.94; N, 4.42

EXAMPLE 2

1 - Benzyl - 3 - (*m* - trifluoromethylbenzoyl) - pyrrolidine hydrochloride.

To a stirred Grignard solution prepared from 32.4 g. (1.3 mole) of magnesium, 300 g. (1.3 mole) of *m* - bromobenzotrifluoride in 450 ml. of ether was added 186 g. (1.0 mole) of 1 - benzyl - 3 - cyanopyrrolidine in 200 ml. of dry ether at a rate which maintained gentle refluxing. The mixture was stirred at reflux for one hour, cooled and treated with a solution of 70 g. (1.3 mole) of ammonium chloride in 600 ml. of water. After the ether was evaporated, the mixture was heated for one hour on a steam-bath to ensure hydrolysis of the ketimine. The mixture was extracted with ether and the combined extracts were washed with water, dried over magnesium sulphate and the solvent evaporated. The residual oil was distilled at reduced pressure and the fraction boiling at 165—167° C./0.07 mm. collected. The light yellow oil weighed 123 g. (37% yield). A portion (23 g.) of the free base was redistilled slowly and the fraction boiling at 148—150° C./0.04 mm. collected. The oil weighed 16 g. A portion (10 g.) of the oil was dissolved in ether and treated with ethereal hydrogen chloride. The white hydrochloride which formed melted at 158—160.5° C. and weighed 9.8 g. after it was recrystallized from methyl ethyl ketone.

Analysis: Calculated for $C_{19}H_{19}NOClF_3$:
C, 61.70; H, 5.18; N, 3.79

40 Found: C, 61.75; H, 5.15; N, 3.99

EXAMPLE 3

1 - Benzyl - 3 - (*p* - fluorobenzoyl) - pyrrolidine hydrochloride.

To a stirred Grignard solution prepared from 42.5 g. (1.76 mole) of magnesium, 308 g. (1.76 mole) of *p* - fluorobromobenzene in 700 ml. of ether was added 164 g. (0.88 mole) of 1 - benzyl - 3 - cyanopyrrolidine in 100 ml. of dry ether at a rate which maintained gentle refluxing. The mixture was stirred for one hour at ambient temperature, cooled and treated with a solution of 94 g. (1.8 moles) of ammonium chloride in 500 ml. of water. The resulting suspension was stirred and heated on a steam bath for 16 hours, cooled and treated with 500 g. of 50% NaOH. Toluene was added to the flask and the mixture was heated for one hour on a steam bath to ensure hydrolysis of the ketimine. The suspension was filtered and the cake washed with toluene. The organic layer was separated,

washed with water and dried over magnesium sulphate. The solvent was evaporated and the residual oil was distilled at reduced pressure. The fraction boiling at 169—170° C./0.05 mm. weighed 103 g. (41% yield). A portion of the free base (7.6 g.) was dissolved in isopropyl ether and treated with ethereal hydrogen chloride. The salt weighed 5.3 g. and melted at 163—165° C. after it was recrystallized from an isopropanol-isopropyl ether mixture.

Analysis: Calculated for $C_{18}H_{19}ClFNO$:
C, 67.60; H, 5.99; N, 4.38

Found: C, 67.82; H, 5.95; N, 4.54

EXAMPLE 4

3 - Benzoyl - 1 - carbamoylpyrrolidine.

To a stirred solution of 68.8 g. (0.65 mole) of cyanogen bromide in one litre of chloroform was added 148 g. (0.56 mole) of 1 - benzyl - 3 - benzoylpyrrolidine (which may be prepared as described for the free base in Example 1) in 200 ml. of chloroform over a period of five hours. After the addition was complete, the solution was refluxed for one hour and then the solvent was evaporated at reduced pressure. The residual oil was treated with 1600 ml. of 4N HCl and refluxed for 16 hours. The mixture was cooled and extracted with ether. The aqueous layer was treated with NaOH and then extracted with chloroform. The chloroform was evaporated and the residual oil which crystallized on cooling was recrystallized from ethyl acetate using charcoal. The product weighed 57 g. (58% yield). The material melted at 127.5—128.5° C. after it was recrystallized from ethyl acetate.

Analysis: Calculated for $C_{17}H_{17}N_2O_2$:
C, 66.03; H, 6.46; N, 12.83

Found: C, 65.83; H, 6.48; N, 12.71

EXAMPLE 5

1 - Carbamoyl - 3 - (*p* - fluorobenzoyl) - pyrrolidine.

To a stirred solution of 44.6 g. (0.43 mole) of cyanogen bromide in 400 ml. of chloroform was added 95 g. (0.33 mole) of 1 - benzyl - 3 - (*p* - fluorobenzoyl) - pyrrolidine (which may be prepared as described for the free base in Example 3) in 100 ml. of chloroform over a period of five hours. After the addition was complete, the solution was refluxed for 1.5 hours and then the solvent was evaporated at reduced pressure. The residual oil was treated with 1600 ml. of 4N HCl and refluxed for 16 hours. The mixture was cooled and extracted with ether. The aqueous layer was made basic with NaOH and then extracted with chloroform. The chloroform was evaporated and the residual oil crystallized on cooling. The crystalline product weighed 32 g. (41% yield) after it was triturated with ethyl acetate and dried. The product was recrystal-

lized from ethyl acetate-ethanol and the white crystalline material melted at 136.5—137.5° C.

5 Analysis: Calculated for $C_{12}H_{11}FN_2O_2$:
C, 61.01; H, 5.54; N, 11.86
Found: C, 61.09; H, 5.41; N, 11.61

EXAMPLE 6

1 - Carbamoyl - 3 - (*m* - trifluoromethyl - benzoyl) - pyrrolidine.

10 A mixture of 1.0 g. (0.004 mole) of 3 - (*m* - trifluoromethylbenzoyl) - pyrrolidine (which may be prepared as described for the free base in Example 2), 0.51 g. (0.005 mole) of nitrourea and 25 ml. of 95% ethanol was heated at about 60° C. until the evolution of
15 gas ceased. After the solvent was evaporated the residue which crystallized on cooling was recrystallized from an ethyl acetate-isopropyl ether mixture. The white product melted at
20 130—131.5° C. and weighed 0.4 g. (35% yield).

Analysis: Calculated for $C_{12}H_{10}F_3N_2O_2$:
C, 54.55; H, 4.58; N, 9.79
Found: C, 54.33; H, 4.56; N, 9.65

EXAMPLE 7

25 3 - Benzoylpyrrolidine hydrochloride hydrate

A solution of 18 g. of 3 - benzoyl - 1 - carbamoylpyrrolidine (which may be prepared as in Example 4) in 120 ml. of concentrated
30 HCl was refluxed three days, cooled and made basic with 50% NaOH. The oil which separated was extracted with benzene and the combined extracts were washed with water, dried
35 over magnesium sulphate and the solvent evaporated. The residual oil weighed 8.1 g. (53% yield). A portion of the free base (5.0 g.) was dissolved in isopropanol and treated with ethereal HCl. The salt which formed was
40 recrystallized from an isopropanol-ether mixture. The product weighed 2.5 g. and melted at 59—61° C.

Analysis: Calculated for $C_{11}H_{16}NO_2Cl$:
C, 57.51; H, 7.02; N, 6.10
Found: C, 57.73; H, 6.80; N, 6.22

EXAMPLE 8

45 3 - (*p* - Fluorobenzoyl) - pyrrolidine oxalate.

A mixture of 50 g. of 1 - carbamoyl - 3 - (*p* - fluorobenzoyl) - pyrrolidine (which may be prepared as in Example 5) in 400 ml. of
50 conc. HCl was refluxed three days, cooled and made basic with 50% NaOH. The oil which separated was extracted with benzene and the combined extracts were washed with water, dried over magnesium sulphate and the solvent evaporated. The residual oil
55 weighed 19.0 g. (46% yield). A portion (1.9 g., 0.01 mole) of the free base was dissolved in isopropanol and treated with 1.3 g. (0.01

mole) of oxalic acid dihydrate and heated 60 several minutes. The crystalline salt which separated on cooling was recrystallized again from the same solvent. The salt weighed 1.8 g. and melted at 116—119° C. (rapid heating). When the salt was heated slowly it
65 softened at 115—117° C. and melted at 120—124° C.

Analysis: Calculated for $C_{13}H_{14}FNO_4$:
C, 55.12; H, 4.98; N, 4.95
Found: C, 55.40; H, 5.01; N, 4.99 70

EXAMPLE 9

3 - (*m* - Trifluoromethylbenzoyl) - pyrrolidine oxalate.

To a stirred solution of 44.6 g. (0.043 mole) of cyanogen bromide in 400 ml. of
75 chloroform was added over a period of four hours, 102 g. (0.31 mole) of 1 - benzyl - 3 - (*m* - trifluoromethylbenzoyl - pyrrolidine (which may be prepared as described for the free base in Example 2). After the addition
80 was complete, the mixture was heated at reflux for one hour and then the solvent was evaporated at reduced pressure. An acidic solution of the residual oil in 1200 ml. of 3N hydrochloric acid was refluxed for 24 hours. The
85 cooled acidic solution was decanted from a dark viscous residue and made basic with 25% sodium hydroxide and the basic solution extracted with benzene. The combined
90 extracts were washed with water, dried over magnesium sulphate and the solvent evaporated. A solution of the residual oil (the free base) (24 g., 0.1 mole) in isopropyl ether was treated with a solution of 12.6 g. (0.10
95 mole) of oxalic acid dihydrate in methanol. The crude salt which formed was recrystallized from isopropanol yielding 7.0 g. (7% yield) of product melting at 86—87° C.

Analysis: Calculated for $C_{11}H_{11}F_3NO_4$:
C, 50.45; H, 4.23; N, 4.20
Found: C, 50.33; H, 4.29; N, 4.47 100

EXAMPLE 10

1 - (*N* - methylcarbamoyl) - 3 - (*m* - (trifluoromethylbenzoyl)pyrrolidine

To a stirred solution of 2.0 g. (0.0082 mole) of 3 - (*m* - trifluoromethylbenzoyl)pyrrolidine (which may be prepared as described for the free base in Example 9) in 50 ml. of dry
105 benzene was added slowly a solution of 0.57 g. (0.01 mole) of methyl isocyanate in 15 ml. of dry benzene. After the addition was completed, the solution was stirred for 30 minutes at room temperature. The solvent was eva-
110 porated at reduced pressure and the residual oil which crystallized on cooling was recrystallized from isopropyl ether. The white product melted at 102—103.5° C. and weighed 1.8 g. (68% yield).

Analysis: Calculated for $C_{11}H_{10}N_2O_2F_3$:
C, 56.00; H, 5.04; N, 9.33
Found: C, 56.27; H, 5.07; N, 9.25

Using the procedure described in Example 10, the following compounds were prepared from the stated starting materials:

1 - (N - phenylcarbamoyl) - 3 - benzoyl - pyrrolidine by reacting 3 - benzoylpyrrolidine (which may be prepared as described for the free base in Example 7) and phenyl isocyanate.
10 1 - [N - (p - tolyl) - carbamoyl] - 3 - benzoylpyrrolidine by reacting p-tolyl isocyanate and 3 - benzoylpyrrolidine.

15 1 - (N - phenylcarbamoyl) - 3 - (p - fluoro - benzoyl) - pyrrolidine by reacting 3 - (p - fluorobenzoyl) - pyrrolidine (which may be prepared as described for the free base in Example 8) and phenyl isocyanate.

20 1 - [N - (m - trifluoromethylphenyl) - carbamoyl] - 3 - benzoylpyrrolidine by reacting 3 - benzoylpyrrolidine and m - trifluoromethylphenyl isocyanate.

25 1 - [N - (m - chlorophenyl) - carbamoyl] - 3 - benzoylpyrrolidine by reacting 3 - benzoylpyrrolidine and m - chlorophenyl isocyanate.

EXAMPLE 11

N - Cyclopentyl - N - (p - chlorophenyl) - carbamoyl chloride.
30 N - Cyclopentyl - p - chloroaniline (78.4 gms., 0.4 mole) was added slowly with stirring to a cold (10° C.) toluene solution of 60 gms. (0.6 mole) of phosgene. The reaction mixture was stirred one and one-half hours at room
35 temperature, then stirred at 85° C. for four hours, cooled, filtered, and the filtrate concentrated under reduced pressure to give 90 grams of crude material. The crude material was crystallized from ligroin (60—90° C.) to
40 give 85.5 grams of white crystalline N - cyclopentyl - N - (p - chlorophenyl) - carbamoyl chloride melting at 82—85° C.

EXAMPLE 12

45 N - Methyl - N - phenylcarbamoyl chloride.

Using the method of Example 11, N - methyl - aniline was mixed and reacted with phosgene to give N - methyl - N - phenyl - carbamoyl chloride melting at 85—86.5° C.

EXAMPLE 13

50 N - Cyclopentyl - N - phenylcarbamoyl chloride.

Using the method of Example 11, N - cyclopentylaniline was mixed and reacted with
55 phosgene to give N - cyclopentyl - N - phenylcarbamoyl chloride melting at 77.5—79.5° C.

Using the procedure described in Example 11, the following compounds were prepared
60 from the stated starting materials:

N, N - diphenylcarbamoyl chloride by reacting diphenylamine and phosgene.

N, N - di - (p - tolyl) - carbamoyl chloride by reacting di - p - tolylamine and phosgene.

N, N - diethylcarbamoyl chloride by reacting diethylamine and phosgene. 65

EXAMPLE 14

1 - (N - cyclopentyl - N - phenylcarbamoyl) - 3 - benzoylpyrrolidine.

To a stirred solution of 35 gms. (0.20 mole) of 3 - benzoylpyrrolidine in 150 ml. of dry toluene was added dropwise a solution of 44.6 gms. (0.20 mole) of N - cyclopentyl - N - phenylcarbamoyl chloride (which may be prepared as in Example 13) in 200 ml. of dry toluene. The reaction mixture was stirred at room temperature for two hours following the addition and then slowly raised to the reflux temperature where it was maintained for six hours. Following the reflux period the reaction mixture was cooled, washed with water, dried over sodium sulphate and the toluene stripped from the dry solution under reduced pressure to give the product 1 - (N - cyclopentyl - N - phenylcarbamoyl) - 3 - benzoylpyrrolidine as a white crystalline solid. 70 75 80 85

Using the procedure described above, the following compounds were prepared from the stated starting materials: 90

1 - (N, N - diphenylcarbamoyl) - 3 - benzoylpyrrolidine was prepared by reacting N, N - diphenylcarbamoyl chloride (which may be prepared as in Example 13) with 3 - benzoylpyrrolidine. 95

1 - (N, N - diphenylcarbamoyl) - 3 - (p - fluorobenzoyl) - pyrrolidine was prepared by reacting N, N - diphenylcarbamoyl chloride with 3 - (p - fluorobenzoyl) - pyrrolidine.

1 - (N, N - diethylcarbamoyl) - 3 - (p - fluorobenzoyl) - pyrrolidine was prepared by reacting N, N - diethylcarbamoyl chloride (which may be prepared as in Example 13) with 3 - (p - fluorobenzoyl) - pyrrolidine. 100

1 - (N - methyl - N - phenylcarbamoyl) - 3 - (m - trifluoromethylbenzoyl) - pyrrolidine was prepared by reacting N - methyl - N - phenylcarbamoyl chloride (which may be prepared as in Example 12) with 3 - (m - trifluoromethylbenzoyl) - pyrrolidine. 105 110

1 - (N - cyclopentyl - N - phenylcarbamoyl) - 3 - (m - trifluoromethylbenzoyl) - pyrrolidine was prepared by reacting N - cyclopentyl - N - phenylcarbamoyl chloride with 3 - (m - trifluoromethylbenzoyl) - pyrrolidine. 115

Effective quantities of any of the foregoing pharmacologically active compounds may be administered to a living animal body in any of various ways, for example, orally as in capsules or tablets. 120

Although very small quantities of the active

- materials of the present invention, even as low as 0.1 milligram, are effective when minor therapy is involved or in cases of administration to subjects having a relatively low body weight, unit dosages are usually five milligrams or above and preferably twenty-five, fifty or one-hundred milligrams. Five to fifty milligrams appear optimum per unit dose, while usual broader ranges appear to be one to 500 milligrams per unit dose. The active agent of the invention may be combined with other pharmacologically active agents, or with buffers or antacids, for administration and the proportion of the active agent in the compositions may be varied widely. It is only necessary that the active ingredients constitute an effective amount, i.e., such that a suitable effective dosage will be obtained consistent with the dosage form employed.
- The formulations given below are representative for the pharmacologically active compounds of the invention.

1) Capsules.

Capsules of 5 mg, 25 mg, and 50 mg of active ingredient per capsule are prepared. With the higher amounts of active ingredient, reduction may be made in the amount of lactose.

Typical Blend for Encapsulation	Per Capsule, mg.	
Active ingredient	5.0	
Lactose	296.7	
Starch	129.0	
Magnesium stearate	4.3	
Total	435.0 mg	35

Other capsule formulations preferably contain a higher dosage of active ingredient, as follows:

Ingredients	100 mg per Capsule	250 mg per Capsule	500 mg per Capsule
Active ingredient	100.0	250.0	500.0
Lactose	231.5	126.5	31.1
Starch	99.2	54.2	13.4
Magnesium stearate	4.3	4.3	5.5
Total	435.0 mg.	435.0 mg.	550.0 mg.

In each case, uniformly blend the selected active ingredient with lactose, starch, and magnesium stearate and encapsulate the blend.

stearate and this blend is then converted into tablets on a suitable tablet press.

2) Tablets

- A typical formulation for a tablet containing 5.0 mg of active ingredient per tablet follows. The formulation may be used for other strengths of active ingredient by adjustment of weight of dicalcium phosphate.

	Per Tablet mg.
1. Active ingredient	5.0
2. Corn starch	13.6
3. Corn starch (paste)	3.4
4. Lactose	79.2
5. Dicalcium phosphate	68.0
6. Calcium stearate	0.9
Total	170.1 mg.

- Uniformly blend the active ingredient, lactose, milo starch and corn starch. This blend is granulated using water as a granulating medium. The wet granules are passed through an eight mesh screen and dried at 140 to 160° F overnight. The dried granules are passed through a number ten mesh screen and blended with the proper amount of calcium

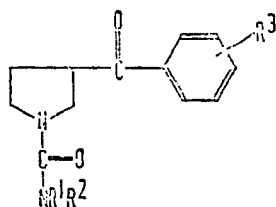
B. 100 mg. Tablet

Ingredient	Per Tablet, mg.	
Active ingredient	100.0	
Lactose	190.0	
Dicalcium phosphate	172.2	
Starch	54.0	
Milo starch	21.6	
Calcium stearate	2.2	
Total	540.0 mg.	80

Uniformly blend the active ingredient, lactose, dicalcium phosphate, starch and milo starch. This blend is granulated with water and the wet mass is passed through a number eight mesh screen. The wet granules are dried at 140 to 160° F overnight. The dried granules are passed through a number ten mesh screen. These dried granules are blended with the proper weight of calcium stearate and the lubricated granules are then converted into tablets on a suitable tablet press.

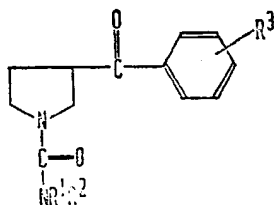
WHAT WE CLAIM IS:—

1. Compounds having the formula:



wherein:

- R^1 and R^2 each represent hydrogen, lower alkyl, lower cycloalkyl or aryl; and
- 5 R^3 represents hydrogen, fluorine, chlorine, bromine, lower alkyl or trifluoromethyl; and acid addition salts of these compounds.
2. 1 - (N - Lower alkyl carbamoyl) - 3 - aroylpyrrolidines.
- 10 3. 1 - (N - Aryl carbamoyl) - 3 - aroyl - pyrrolidines.
4. 1 - Carbamoyl - 3 - benzoylpyrrolidine.
5. 1 - Carbamoyl - 3 - (*p* - fluorobenzoyl) - pyrrolidine.
- 15 6. 1 - Carbamoyl - 3 - (*m* - trifluoromethylbenzoyl) - pyrrolidine.
7. 1 - (N - Methylcarbamoyl) - 3 - (*m* - trifluoromethylbenzoyl) - pyrrolidine.
8. 1 - (N - Cyclopentyl - N - phenyl - carbamoyl - 3 - benzoylpyrrolidine.
- 20 9. 1 - (N - (Cyclopentyl - N - phenyl - carbamoyl) - 3 - (*m* - fluorobenzoyl) - pyrrolidine.
10. A process for the preparation of 1 - carbamoyl - 3 - aroylpyrrolidines having the formula:
- 25



wherein:

R^1 and R^2 each represent hydrogen, lower alkyl, lower cycloalkyl or aryl; and

30 R^3 represents hydrogen, fluorine, chlorine, bromine, lower alkyl or trifluoromethyl; which comprises the steps of:

(1) reacting a 1 - benzyl - 3 - cyanopyrrolidine with an arylmagnesium halide in a dry ether reaction medium;

35

(2) reacting the 1 - benzyl - 3 - aroyl - pyrrolidine obtained in step (1) with cyanogen bromide;

(3) hydrolyzing the 1 - cyano - 3 - aroyl - pyrrolidine from step (2) using dilute hydrochloric acid to a 1 - carbamoyl - 3 - aroyl - pyrrolidine; and optionally (to produce compounds where at least one of R^1 and R^2 is other than hydrogen):

40

(4) hydrolyzing the 1 - carbamoyl - 3 - aroylpyrrolidine from step (3) using concentrated hydrochloric acid to a 3 - aroylpyrrolidine; and

45

(5) reacting the 3 - aroylpyrrolidine from step (3) with a reactant selected from lower alkyl isocyanates, aryl isocyanates, N - lower cycloalkyl - N - arylcarbamoyl halides, N, N - di - lower - alkylcarbamoyl halides and N, N - diarylcarbamoyl halides.

50

11. A process for the preparation of 1 - carbamoyl - 3 - aroylpyrrolidines substantially as described in any of Examples 4 to 6, 10 or 14.

55

12. 1 - Carbamoyl - 3 - aroylpyrrolidines which have been prepared by a process as claimed in Claim 10 or Claim 11.

60

KILBURN & STRODE,
Agents for the Applicants,
Chartered Patent Agents.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1972.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

BEST AVAILABLE COPY